WEST

Generate Collection Print

L4: Entry 28 of 132 File: USPT Jul 9, 2002

DOCUMENT-IDENTIFIER: US 6416740 B1
TITLE: Acoustically active drug delivery systems

Brief Summary Text (10):
Treatment of several diseases would be enhanced with improvements in drug delivery technology. Retinal disease, for example, currently is difficult to treat. No effective treatments are available for the most common diseases. Another ophthalmologic disease, diabetic retinopathy, is a common complication of diabetes. In this disease neovascularization results in a proliferation of blood vessels which destroy the retina. Diabetic retinopathy is treated by medical management of diabetes (better control of blood sugar) and ablating neovascularity with laser photocoagulation.

Detailed Description Text (8):
"Lyophilize" or freeze drying refers to the preparation of a lipid composition in dry form by rapid freezing and dehydration in the frozen state (sometimes referred to as sublimation). Lyophilization takes place at a temperature which results in the crystallization of the lipids to form a lipid matrix. This process may take place under vacuum at a pressure sufficient to maintain frozen product with the ambient temperature of the containing vessel at about room temperature, preferably less than about 500 mTorr, more preferably less than about 200 mTorr, even more preferably less than about 1 mTorr. Due to the small amount of lipids used to prepare the lipid composition of the present invention, lyophilization is not difficult to conduct. The lipid composition in the present invention is an improvement over conventional microsphere compositions because the amount of lipids are reduced in comparison to the prior art and the lipid composition is formulated to minimize loss due to filtration of large (>0.22 .mu.m) particulate matter. The latter is particularly important with lipids having a net negative charge (i.e. phosphatidic acid) because their solubility in aqueous-based diluents is marginal.

Detailed Description Text (12):
"Carrier" refers to a pharmaceutically acceptable vehicle, which is a nonpolar, hydrophobic solvent, and which may serve as a reconstituting medium. The carrier may be aqueous-based or organic-based. Carriers include, inter alia, lipids, proteins, polysaccharides, sugars, polymers, copolymers, and acrylates.

Detailed Description Text (16):
"Stabilizing material" or "stabilizing compound" refers to any material which is capable of improving the stability of compositions containing the gases, gaseous precursors, steroid prodrugs, targeting ligands and/or other bioactive agents described herein, including, for example, mixtures, suspensions, emulsions, dispersions, vesicles, or the like. Encompassed in the definition of "stabilizing material" are certain of the present bioactive agents. The improved stability involves, for example, the maintenance of a relatively balanced condition, and may be exemplified, for example, by increased resistance of the composition against destruction, decomposition, degradation, and the like. In the case of preferred embodiments involving vesicles filled with gases, gaseous precursors, liquids, steroid prodrugs and/or bioactive agents, the stabilizing compounds may serve to either form the vesicles or stabilize the vesicles, in either way serving to minimize or substantially (including completely) prevent the escape of gases, gaseous precursors, steroid prodrugs and/or bioactive agents from the vesicles until said release is desired. The term "substantially," as used in the present context of

preventing escape of gases, gaseous precursors, steroid prodrugs and/or bioactive agents from the vesicles, means greater than about 50% is maintained entrapped in the vesicles until release is desired, and preferably greater than about 60%, more preferably greater than about 70%, even more preferably greater than about 80%, still even more preferably greater than about 90%, is maintained entrapped in the vesicles until release is desired. In particularly preferred embodiments, greater than about 95% of the gases, gaseous precursors, steroid prodrugs and/or bioactive agents are maintained entrapped until release is desired. The gases, gaseous precursors, liquids, steroid prodrugs and/or bioactive agents may also be completely maintained entrapped (i.e., about 100% is maintained entrapped), until release is desired. Exemplary stabilizing materials include, for example, lipids, proteins, polymers, carbohydrates and surfactants. The resulting mixture, suspension, emulsion or the like may comprise walls (i.e., films, membranes and the like) around the steroid prodrug, bioactive agent, gases and/or gaseous precursors, or may be substantially devoid of walls or membranes, if desired. The stabilizing may, if desired, form droplets. The stabilizing material may also comprise salts and/or sugars. In certain embodiments, the stabilizing materials may be substantially (including completely) cross-linked. The stabilizing material may be neutral, positively or negatively charged.

Detailed Description Text (18):
"Vesicle" refers to an entity which is generally characterized by the presence of one or more walls or membranes which form one or more internal voids. Vesicles may be formulated, for example, from a stabilizing material such as a lipid, including the various lipids described herein, a proteinaceous material, including the various proteins described herein, and a polymeric material, including the various polymeric materials described herein. As discussed herein, vesicles may also be formulated from carbohydrates, surfactants, and other stabilizing materials, as desired. The lipids, proteins, polymers and/or other vesicle forming stabilizing materials may be natural, synthetic or semi-synthetic. Preferred vesicles are those which comprise walls or membranes formulated from lipids. The walls or membranes may be concentric or otherwise. The stabilizing compounds may be in the form of one or more monolayers or bilayers. In the case of more than one monolayer or bilayer, the monolayers or bilayers may be concentric. Stabilizing compounds may be used to form a unilamellar vesicle (comprised of one monolayer or bilayer), an oligolamellar vesicle (comprised of about two or about three monolayers or bilayers) or a multilamellar vesicle (comprised of more than about three monolayers or bilayers). The walls or membranes of vesicles may be substantially solid (uniform), or they may be porous or semi-porous. The vesicles described herein include such entities commonly referred to as, for example, liposomes, lipospheres, particles, nanoparticles, micelles, bubbles, microbubbles, microspheres, lipid-coated bubbles, polymer-coated bubbles and/or protein-coated bubbles, microbubbles and/or microspheres, nanospheres, microballoons, microcapsules, aerogels, clathrate bound vesicles, hexagonal H II phase structures, and the like. The internal void of the vesicles may be filled with a wide variety of materials including, for example, water, oil, gases, gaseous precursors, liquids, fluorinated liquids, liquid perfluorocarbons, liquid perfluoroethers, therapeutics, and bioactive agents, if desired, and/or other materials. The vesicles may also comprise a targeting ligand, if desired.

Detailed Description Text (19):
"Liposome" refers to a generally spherical or spheroidal cluster or aggregate of amphipathic compounds, including lipid compounds, typically in the form of one or more concentric layers, for example, bilayers. They may also be referred to herein as lipid vesicles. The liposomes may be formulated, for example, from ionic lipids and/or non-ionic lipids. Liposomes formulated from non-ionic lipids may be referred to as niosomes.

Detailed Description Text (34):
"Targeting ligand" refers to any material or substance which may promote targeting of tissues and/or receptors in vivo or tit vitro with the compositions of the present invention. The targeting ligand may be synthetic, semi-synthetic, or naturally-occurring. Materials or substances which may serve as targeting ligands include, for example, proteins, including antibodies, antibody fragments, hormones, hormone analogues, glycoproteins and lectins, peptides, polypeptides, amino acids, sugars, saccharides, including monosaccharides and polysaccharides, carbohydrates,

vitamins, steroids, steroid analogs, hormones, cofactors, bioactive agents, and genetic material, including nucleosides, nucleotides, nucleotide acid constructs and polynucleotides.

Detailed Description Text (93):
The present compositions are desirably formulated in an aqueous environment which can induce the lipid, because of its hydrophobic-hydrophilic nature, to form vesicles, which may be the most stable configuration which can be achieved in such an environment. The diluents which can be employed to create such an aqueous environment include, for example, water, including deionized water or water containing one or more dissolved solutes, such as salts or sugars, which preferably do not interfere with the formation and/or stability of the vesicles or their use as diagnostic agents, such as ultrasound contrast agents, MRI contrast agents, CT contrast agents and optical imaging contrast agents; and normal saline and physiological saline.

Detailed Description Text (97):
Exemplary lipids which may be used to prepare the present invention include, for example, fatty acids, lysolipids, fluorolipids, phosphocholines, such as those associated with platelet activation factors (PAF) (Avanti Polar Lipids, Alabaster, Ala.), including 1-alkyl-2-acetoyl-sn-glycero 3-phosphocholines, and 1-alkyl-2-hydroxy-sn-glycero 3-phosphocholines, which target blood clots; phosphatidylcholine with both saturated and unsaturated lipids, including dioleoylphosphatidylcholine; dimyristoylphosphatidylcholine; dipentadecanoylphosphatidyl-choline; dilauroylphosphatidylcholine; dipalmitoylphosphatidylcholine (DPPC); distearoylphosphatidylcholine (DSPC); and diarachidonylphosphatidylcholine (DAPC); phosphatidylethanolamines, such as dioleoylphosphatidylethanolamine, dipalmitoylphosphatidylethanolamine (DPPE) and distearoylphosphatidylethanolamine (DSPE); phosphatidylserine; phosphatidylglycerols, including distearoylphosphatidylglycerol (DSPG); phosphatidylinositol; sphingolipids such as sphingomyelin; glycolipids such as ganglioside GM1 and GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acids, such as dipalmitoylphosphatidic acid (DPPA) and distearoylphosphatidic acid (DSPA); palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers, such as chitin, hyaluronic acid, polyvinylpyrrolidone or polyethylene glycol (PEG), also referred to herein as "pegylated lipids" with preferred lipid bearing polymers including DPPE-PEG (DPPE-PEG), which refers to the lipid DPPE having a PEG polymer attached thereto, including, for example, DPPE-PEG5000, which refers to DPPE having attached thereto a PEG polymer having a mean average molecular weight of about 5000; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate and cholesterol hemisuccinate; tocopherol hemisuccinate; lipids with ether and ester-linked fatty acids; polymerized lipids (a wide variety of which are well known in the art); diacetyl phosphate; dicetyl phosphate; stearylamine; cardiolipin; phospholipids with short chain fatty acids of about 6 to about 8 carbons in length; synthetic phospholipids with asymmetric acyl chains, such as, for example, one acyl chain of about 6 carbons and another acyl chain of about 12 carbons; ceramides; non-ionic liposomes including niosomes such as polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohols, polyoxyethylene fatty alcohol ethers, polyoxyalkylene sorbitan fatty acid esters (such as, for example, the class of compounds referred to as TWEEN.TM., commercially available from ICI Americas, Inc., Wilmington, Del.), including polyoxyethylated sorbitan fatty acid esters, glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, polyoxyethylene-polyoxypropylene polymers, and polyoxyethylene fatty acid stearates; sterol aliphatic acid esters including cholesterol sulfate, cholesterol butyrate, cholesterol isobutyrate, cholesterol palmitate, cholesterol stearate, lanosterol acetate, ergosterol palmitate, and phytosterol n-butyrate; sterol esters of sugar acids including cholesterol glucuronide, lanosterol glucuronide, 7-dehydrocholesterol glucuronide, ergosterol glucuronide, cholesterol gluconate, lanosterol gluconate, and ergosterol gluconate; esters of sugar acids and alcohols including lauryl glucuronide, stearoyl glucuronide, myristoyl glucuronide, lauryl gluconate, myristoyl gluconate, and stearoyl gluconate; esters of sugars and aliphatic acids including sucrose laurate, fructose laurate, sucrose palmitate, sucrose stearate, glucuronic acid, gluconic acid and polyuronic acid; saponins including sarsasapogenin, smilagenin, hederagenin, oleanolic acid, and digitoxigenin; glycerol dilaurate, glycerol trilaurate, glycerol dipalmitate, glycerol and glycerol esters including glycerol tripalmitate, glycerol

distearate, glycerol tristearate, glycerol dimyristate, glycerol trimyristate; long chain alcohols including n-decyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, and n-octadecyl alcohol;
6-(5-cholesten-3.beta.-yloxy)-1-thio-.beta.-D-galactopyranoside;
digalactosyldiglyceride;
6-(5-cholesten-3.beta.-yloxy)-hexyl-6-amino-6-deoxy-1-thio-.beta.-D-galact opyranoside;
6-(5-cholesten-3.beta.-yloxy)hexyl-6-amino-6-deoxyl-1-thio-.alpha.-D-manno pyranoside; 12-(((7'-diethylamino-coumarin-3-yl)-carbonyl)-methylamino)-octadecanoic acid; N-[12-(((7'-diethylamino-coumarin-3-yl)-carbonyl)-methylamino)-octadecanoy l]-2-aminopalmitic acid; cholesteryl(4'-trimethyl-ammonio)-butanoate;
N-succinyldioleoylphosphatidylethanol-amine; 1,2-dioleoyl-sn-glycerol;
1,2-dipalmitoyl-sn-3-succinylglycerol; 1,3-dipalmitoyl-2-succinylglycerol;
1-hexadecyl-2-palmitoylglycerophosphoethanolamine and palritoylhomocysteine, and/or any combinations thereof.

Detailed Description Text (127):
Other preferred therapeutics include genetic material such as nucleic acids, RNA, and DNA, of either natural or synthetic origin, including recombinant RNA and DNA and antisense RNA and DNA. Types of genetic material that may be used include, for example, genes carried on expression vectors such as plasmids, phagemids, cosmids, yeast artificial chromosomes (YACs), and defective or "helper" viruses, antigene nucleic acids, both single and double stranded RNA and DNA and analogs thereof, such as phosphorothioate and phosphorodithioate oligodeoxynucleotides. Additionally, the genetic material may be combined, for example, with proteins or other polymers. Examples of genetic material that may be applied using the liposomes of the present invention include, for example, DNA encoding at least a portion of LFA-3, DNA encoding at least a portion of an HLA gene, DNA encoding at least a portion of dystrophin, DNA encoding at least a portion of CFTR, DNA encoding at least a portion of IL-2, DNA encoding at least a portion of TNF, and an antisense oligonucleotide capable of binding the DNA encoding at least a portion of Ras.

Detailed Description Text (161):
The gases and/or gaseous precursors are preferably incorporated in the targeted therapeutic delivery systems irrespective of the physical nature of the composition. Thus, it is contemplated that the gases and/or gaseous precursors may be incorporated, for example, in a surfactant randomly, such as emulsions, dispersions or suspensions, as well as in carriers, including vesicles which are formulated from lipids, such as micelles and liposomes. Incorporation of the gases and/or gaseous precursors in the surfactant may be achieved by using any of a number of methods. For example, in the case of vesicles based on lipids, the formation of gas filled vesicles can be achieved by shaking or otherwise agitating an aqueous mixture which comprises a gas and/or gaseous precursor and one or more lipids. This promotes the formation of stabilized vesicles within which the gas and/or gaseous precursor is encapsulated.

Detailed Description Text (163):
Embodiments include the gases and/or gaseous precursors incorporated in vesicle compositions, with micelles and liposomes being preferred. Vesicles in which a gas or gaseous precursor or both are encapsulated are advantageous in that they provide improved reflectivity in vivo.

Detailed Description Text (179):
A wide variety of methods are available for the preparation of the targeted therapeutic delivery system including vesicles, such as micelles and/or liposomes. Included among these methods are, for example, shaking, drying, gas-installation, spray drying, and the like. Suitable methods for preparing vesicle compositions are described, for example, in U.S. Pat. No. 5,469,854, the disclosure of which is hereby incorporated herein by reference in its entirety. The vesicles are preferably prepared from lipids which remain in the gel state.

Detailed Description Text (181):
In liposomes, the lipid compound(s) may be in the form of a monolayer or bilayer, and the monolayer or bilayer lipids may be used to form one or more monolayers or bilayers. In the case of more than one monolayer or bilayer, the monolayers or

bilayers are generally concentric. Thus, lipids may be used to form unilamellar liposomes (comprised of one monolayer or bilayer), oligolamellar liposomes (comprised of two or three monolayers or bilayers) or multilamellar liposomes (comprised of more than three monolayers or bilayers).

Detailed Description Text (182):
A wide variety of methods are available in connection with the preparation of vesicles, including liposomes. Accordingly, liposomes may be prepared using any one of a variety of conventional liposomal preparatory techniques which will be apparent to those skilled in the art, including, for example, solvent dialysis, French press, extrusion (with or without freeze-thaw), reverse phase evaporation, simple freeze-thaw, sonication, chelate dialysis, homogenization, solvent infusion, microemulsification, spontaneous formation, solvent vaporization, solvent dialysis, French pressure cell technique, controlled detergent dialysis, and others, each involving the preparation of the vesicles in various fashions. See, e.g., Madden et al., Chemistry and Physics of Lipids, 53:37-46 (1990), the disclosure of which is hereby incorporated herein by reference in its entirety. Suitable freeze-thaw techniques are described, for example, in International Application Serial No. PCT/US89/05040, filed Nov. 8, 1989, the disclosure of which is hereby incorporated herein by reference in its entirety. Methods which involve freeze-thaw techniques are preferred in connection with the preparation of liposomes. Preparation of the liposomes may be carried out in a solution, such as an aqueous saline solution, aqueous phosphate buffer solution, or sterile water. The liposomes may also be prepared by various processes which involve shaking or vortexing, which may be achieved, for example, by the use of a mechanical shaking device, such as a Wig-L-Bug.TM. (Crescent Dental, Lyons, Ill.), a Mixomat, sold by Degussa AG, Frankfurt, Germany, a Capmix, sold by Espe Fabrik Pharmazeutischer Praeparate GMBH & Co., Seefeld, Oberay Germany, a Silamat Plus, sold by Vivadent, Lechtenstein, or a Vibros, sold by Quayle Dental, Sussex, England. Conventional microemulsification equipment, such as a Microfluidizer.TM. (Microfluidics, Woburn, Mass.) may also be used.

Detailed Description Text (184):
Many liposomal preparatory techniques which may be adapted for use in the preparation of vesicle compositions are discussed, for example, in U.S. Pat. Nos. 4,728,578, 4,728,575, 4,737,323, 4,533,254, 4,162,282, 4,310,505, and 4,921,706; U.K. Patent Application GB 2193095 A; International Application Serial No. PCT/US85/01161; Mayer et al., Biochimica et Biophysica Acta, 858:161-168 (1986); Hope et al., Biochimica et Biophysica Acta, 812:55-65 (1985); Mayhew et al., Methods in Enzymology, 149:64-77 (1987); Mayhew et al., Biochimica et Biophysica Acta, 755:169-74 (1984); Cheng et al, Investigative Radiology, 22:47-55 (1987); International Application Serial No. PCT/US89/05040; and Liposome Technology, Gregoriadis, ed., Vol. I, pp. 29-31, 51-67 and 79-108 (CRC Press Inc., Boca Raton, Fla. 1984), the disclosures of each of which are hereby incorporated by reference herein in their entirety.

Detailed Description Text (185):
In connection with stabilizing materials, and especially lipid compositions in the form of vesicles, it may be advantageous to prepare the lipid compositions at a temperature below the gel to liquid crystalline phase transition temperature of the lipids. This phase transition temperature is the temperature at which a lipid bilayer will convert from a gel state to a liquid crystalline state. See, for example, Chapman et al., J. Biol. Chem., 249:2512-2521 (1974), the disclosure of which is hereby incorporated by reference herein in its entirety. It is generally believed that vesicles which are prepared from lipids that possess higher gel state to liquid crystalline state phase transition temperatures tend to have enhanced impermeability at any given temperature. See Derek Marsh, CRC Handbook of Lipid Bilayers (CRC Press, Boca Raton, Fla. 1990), at p. 139 for main chain melting transitions of saturated diacyl-sn-glycero-3-phosphocholines. The gel state to liquid crystalline state phase transition temperatures of various lipids will be readily apparent to those skilled in the art and are described, for example, in Gregoriadis, ed., Liposome Technology, Vol. I, 1-18 (CRC Press, 1984). The following table lists some of the representative lipids and their phase transition temperatures.

Detailed Description Text (192):
The required duration of shaking time may be determined by detection of the formation

of foam. For example, 10 ml of lipid solution in a 50 ml centrifuge tube may be vortexed for approximately 15-20 minutes or until the viscosity of the gas filled liposomes becomes sufficiently thick so that it no longer clings to the side walls as it is swirled. At this time, the foam may cause the solution containing the gas filled liposomes to raise to a level of 30 to 35 ml.

Detailed Description Text (193):
The concentration of lipid required to form a preferred foam level will vary depending upon the type of lipid used, and may be readily determined by one skilled in the art, in view of the present disclosure. For example, in preferred embodiments, the concentration of 1,2-dipalmitoylphosphatidylcholine (DPPC) used to form gas filled liposomes according to the methods of the present invention is about 20 mg/ml to about 30 mg/ml saline solution. The concentration of distearoylphosphatidylcholine (DSPC) used in preferred embodiments is about 5 mg/ml to about 10 mg/ml saline solution.

Detailed Description Text (243):
Conventional, aqueous-filled liposomes of the prior art are routinely formed at a temperature above the phase transition temperature of the lipids used to make them, since they are more flexible and thus useful in biological systems in the liquid crystalline state. See, for example, Szoka and Papahadjopoulos, Proc. Natl. Acad. Sci. (1978) 75:4194-4198. In contrast, the vesicles made according to certain preferred embodiments described herein are gaseous precursor filled, which imparts greater flexibility, since gaseous precursors after gas formation are more compressible and compliant than an aqueous solution.

Detailed Description Text (263):
As with the preparation of stabilizing materials and/or vesicles, a wide variety of techniques are available for the preparation of stabilizing materials comprising bioactive agents (which includes steroid prodrugs and targeting ligands). For example, the stabilizing materials and/or vesicle compositions may be prepared from a mixture of lipid compounds, bioactive agents and gases and/or gaseous precursors. In this case, lipid compositions are prepared as described above in which the compositions also comprise bioactive agents. Thus, for example, micelles can be prepared in the presence of a bioactive agent. In connection with lipid compositions which comprise a gas, the preparation can involve, for example, bubbling a gas directly into a mixture of the lipid compounds and one or more additional materials. Alternatively, the lipid compositions may be pre-formed from lipid compounds and gas and/or gaseous precursor. In the latter case, the bioactive agent is then added to the lipid composition prior to use. For example, an aqueous mixture of liposomes and gas may be prepared to which the bioactive agent is added and which is agitated to provide the liposome composition. The liposome composition can be readily isolated since the gas and/or bioactive agent filled liposome vesicles generally float to the top of the aqueous solution. Excess bioactive agent can be recovered from the remaining aqueous solution.

Detailed Description Text (294):
The invention is useful in delivering bioactive agents to a patient's lungs. For pulmonary applications of the steroid prodrugs, dried or lyophilized powdered liposomes may be administered via inhaler. Aqueous suspensions of liposomes or micelles, preferably gas/gaseous precursor filled, may be administered via nebulization. Gas filled liposomes of the present invention are lighter than, for example, conventional liquid filled liposomes which generally deposit in the central proximal airway rather than reaching the periphery of the lungs. It is therefore believed that the gas filled liposomes of the present invention may improve delivery of a bioactive agent to the periphery of the lungs, including the terminal airways and the alveoli. For application to the lungs, the gas filled liposomes may be applied through nebulization.

Detailed Description Text (295):
In applications such as the targeting of the lungs, which are lined with lipids, the bioactive agent may be released upon aggregation of the gas filled liposomes with the lipids lining the targeted tissue. Additionally, the gas filled liposomes may burst after administration without the use of ultrasound. Thus, ultrasound need not be applied to release the drug in the above type of administration. For vascular

administration the steroid prodrugs are generally injected into the venous system as a formulation vehicle, e.g. preferably gas or gaseous precursor containing liposomes.

Detailed Description Text (299):
Generally, the steroid prodrugs, stabilizing materials and/or vesicles of the invention are administered in the form of an aqueous suspension such as in water or a saline solution (e.g., phosphate buffered saline). Preferably, the water is sterile. Also, preferably the saline solution is an isotonic saline solution, although, if desired, the saline solution may be hypotonic (e.g., about 0.3 to about 0.5% NaCl). The solution may be buffered, if desired, to provide a pH range of about 5 to about 7.4. Preferably, dextrose or glucose is included in the media. Other solutions that may be used for administration of gas filled liposomes include, for example, almond oil, corn oil, cottonseed oil, ethyl oleate, isopropyl myristate, isopropyl palmitate, mineral oil, myristyl alcohol, octyldodecanol, olive oil, peanut oil, persic oil, sesame oil, soybean oil, and squalene.

Detailed Description Text (300):
The size of the stabilizing materials and/or vesicles of the present invention will depend upon the intended use. With smaller liposomes, resonant frequency ultrasound will generally be higher than for the larger liposomes. Sizing also serves to modulate resultant liposomal biodistribution and clearance. In addition to filtration, the size of the liposomes can be adjusted, if desired, by procedures known to one skilled in the art, such as shaking, microemulsification, vortexing, filtration, repeated freezing and thawing cycles, extrusion, extrusion under pressure through pores of a defined size, sonication, homogenization, the use of a laminar stream of a core of liquid introduced into an immiscible sheath of liquid. See, for example, U.S. Pat. Nos. 4,728,578, 4,728,575, 4,737,323, 4,533,254, 4,162,282, 4,310,505 and 4,921,706; U.K. Patent Application GB 2193095 A; International Applications PCT/US85/01161 and PCT/US89/05040; Mayer et al., Biochimica et Biophysica Acta, 858:161-168 (1986); Hope et al., Biochimica et Biophysica Acta, 812:55-65 (1985); Mayhew et al., Methods in Enzymology, 149:64-77 (1987); Mayhew et al., Biochimica et Biophysica Acta, 755:169-74 (1984); Cheng et al, Investigative Radiology, 22:47-55 (1987); and Liposomes Technology, Gregoriadis, G., ed., Vol. 1, pp. 29-37, 51-67 and 79-108 (CRC Press Inc, Boca Raton, Fla., 1984). The disclosures of each of the foregoing patents, publications and patent applications are hereby incorporated by reference herein in their entirety. Extrusion under pressure through pores of defined size is a preferred method of adjusting the size of the liposomes.

Detailed Description Text (302):
For in vitro use, such as cell culture applications, the gas filled vesicles may be added to the cells in cultures and then incubated. Subsequently sonic energy can be applied to the culture media containing the cells and liposomes.

Detailed Description Text (311):
For therapeutic drug delivery, the rupturing of the bioactive agent containing the targeted therapeutic delivery systems of the invention is surprisingly easily carried out by applying ultrasound of a certain frequency to the region of the patient where therapy is desired, after the liposomes have been administered to or have otherwise reached that region, e.g., via delivery with targeting ligands. Specifically, it has been unexpectedly found that when ultrasound is applied at a frequency corresponding to the peak resonant frequency of the bioactive agent containing gas filled vesicles, the vesicles will rupture and release their contents. The peak resonant frequency can be determined either in vivo or in vitro, but preferably in vivo, by exposing the stabilizing materials or vesicles, including liposomes, to ultrasound, receiving the reflected resonant frequency signals and analyzing the spectrum of signals received to determine the peak, using conventional means. The peak, as so determined, corresponds to the peak resonant frequency, or second harmonic, as it is sometimes termed.

Detailed Description Text (312):
Preferably, the compositions of the invention have a peak resonant frequency of between about 0.5 and about 10 MHz. Of course, the peak resonant frequency of the gas filled vesicles of the invention will vary depending on the outside diameter and, to some extent, the elasticity or flexibility of the liposomes, with the larger and more

elastic or flexible liposomes having a lower resonant frequency than the smaller and less elastic or flexible vesicles.

Detailed Description Text (318):
To use the phenomenon of cavitation to release and/or activate the prodrugs within the gas filled stabilizing materials and/or vesicles, lower frequency energies may be used, as cavitation occurs more effectively at lower frequencies. Using a 0.757 MHz transducer driven with higher voltages (as high as 300 volts) cavitation of solutions of gas-filled liposomes will occur at thresholds of about 5.2 atmospheres.

Detailed Description Text (319):
The table below shows the ranges of energies transmitted to tissues from diagnostic ultrasound on commonly used instruments such as the Piconics Inc. (Tyngsboro, Mass.) Portascan general purpose scanner with receiver pulser 1966 Model 661; the Picker (Cleveland, Ohio) Echoview 8L Scanner including 80C System or the Medisonics (Mountain View, Calif.) Model D-9 Versatone Bidirectional Doppler. In general, these ranges of energies employed in pulse repetition are useful for diagnosis and monitoring gas-filled liposomes but are insufficient to rupture the gas-filled liposomes of the present invention.

Detailed Description Text (320):
Either fixed frequency or modulated frequency ultrasound may be used. Fixed frequency is defined wherein the frequency of the sound wave is constant over time. A modulated frequency is one in which the wave frequency changes over time, for example, from high to low (PRICH) or from low to high (CHIRP). For example, a PRICH pulse with an initial frequency of 10 MHz of sonic energy is swept to 1 MHz with increasing power from 1 to 5 watts. Focused, frequency modulated, high energy ultrasound may increase the rate of local gaseous expansion within the liposomes and rupturing to provide local delivery of therapeutics.

Detailed Description Text (323):
A gas filled vesicle filled with oxygen gas should create extensive free radicals with cavitation. Also, metal ions from the transition series, especially manganese, iron and copper can increase the rate of formation of reactive oxygen intermediates from oxygen. By encapsulating metal ions within the vesicles, the formation of free radicals in vivo can be increased. These metal ions may be incorporated into the liposomes as free salts, as complexes, e.g., with EDTA, DTPA, DOTA or desferrioxamine, or as oxides of the metal ions. Additionally, derivatized complexes of the metal ions may be bound to lipid head groups, or lipophilic complexes of the ions may be incorporated into a lipid bilayer, for example. When exposed to thermal stimulation, e.g., cavitation, these metal ions then will increase the rate of formation of reactive oxygen intermediates. Further, radiosensitizers such as metronidazole and misonidazole may be incorporated into the gas filled vesicles to create free radicals on thermal stimulation.

Detailed Description Text (334):
The procedure used in Example 1 was followed, adding 0.5 units/ml of urokinase (Sigma Chemical Co., St. Louis, Mo.) to the labeled DPPE in the experimental sample. Data presented below show effectiveness of entrappment in soybean AALs. The numbers represent a fluorescence measurement (proporational to the amount of labelled DPPE that releases into solution indicating liposome rupture.)

Detailed Description Text (335):
The data shows that soybean oil and urokinase somewhat stabilize the lipid vesicle from rupture and provide a good indication that urokinase incorporates into the AAL as well as into a conventional liposome.

Detailed Description Text (367):
One gram of .alpha.-tocopherol, 1.0 gram of retinoic acid and 3 grams of soybean oil are agitated in a vortex mixer. To this mixture is added 1.0 g. of a lipid blend consisting of 82 mol percent DPPC, 10 mol percent DPPA and 8 mol percent DPPE-PEG5000 (all phospholipids from Avanti Polar Lipids, Alabaster, Ala.). The mixture is stirred 10 minutes at 50.degree. C. then transferred into a container with 200 mls normal saline plus 1% w/v Pluronic F-65 and emulsified with a Microfluidizer (10.times.) at 16,000 psi while the temperature is maintained at 50.degree. C. The material is then

subdivided into 1.0 ml aliquots in 1.5 ml vials. The vials are vacuum-evacuated, and the headspace is filled with perfluorobutane. The resulting product is a suspension of drug in oil filled liposomes or lipospheres containing about 0.45% by weight a-tocopherol and 0.45% by weight retinoic acid. The vials are sealed and placed on a Wig-L-Bug (Crescent Dental, Lyons Ill.) and agitated at 2800 rpm for 2 minutes. The final product consists of acoustically active lipospheres instilled with perfluorobutane gas, with a mean diameter under 10 .mu.m. The product can be injected in this form or filtered to eliminate particles over 2 .mu.m just prior to injection.

Other Reference Publication (54):
Mayhew et al., "High-Pressure Continuous-Flow System for Drug Entrapment in Liposomes", Methods in Enzymology, 1987, 149, 64-77.

Other Reference Publication (55):
Mayhew et al., "Characterization of Liposomes Prepared Using a Microemulsifier", Biochim. et Biophys. Acta, 1984, 775, 169-174.

Other Reference Publication (58):
Cheng et al., "The Production and Evaluation of Contrast-Carrying Liposomes Made with an Automatic High Pressure System", Invest. Radiol., 1987, 22, 47-55.

Other Reference Publication (71):
Scarpa et al., "Cation Permeability of Liposomes as a Function of the Chemical Composition of the Lipid Bilayers", Biochimica et Biophysica Acta, 1971, 241, 789-797.

Other Reference Publication (77):
Chapman D., "Physiochemical Properties of Phospholipids and Lipid Water Systems", Liposome Technology, Gregoriadis, G., (ed.), CRC Press, Boca Raton, FL, 1984, 1, 1-18.

Other Reference Publication (81):
Ostro, M. (ed.), "Liposomes", Marcel Dekker, Inc., New York, 1983, 102-103.

Other Reference Publication (86):
Vion-Dury, J. et al., "Liposome-Mediated Delivery of Gadolinium Diethylenetriaminepentaacetic Acid to Hepatic Cells a Phosphorus-31 NMR Study", J. Pharmacol. Exper. Ther., 1989, 250(3), 1113-1118 (abstract).

Other Reference Publication (87):
Zalutsky, M.R. et al., "Characterization of Liposomes Containing Iodine-125-Labeled Radiographic Contrast Agents", Invest. Radiol., 1987, 22(2), 141-147 (abstract).

Other Reference Publication (88):
Crowe et al., "Preservation of Freeze-Dried Liposomes by Trehalose", Archives Biochem. Biophys., 1985, 242(1), 240-247.

Other Reference Publication (91):
Gregoriadis, G., (Ed.), "Preparation of Liposomes", Liposome Technology, vol. I, CRC Press, Inc., Boca Raton, FL, 1984, 1-18, 30-35, 51-65 and 79-107.

Other Reference Publication (97):
Hug et al., "Liposomes for the Transformation of Eukaryotic Cells", Biochim. et Biophys. Acta, 1991, 1097, 1-17.

Other Reference Publication (99):
Szoka et al., "Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaportion", Proc. Natl. Acad. Sci. USA, 1978, 75(9), 4194-4198.

Other Reference Publication (104):
deGier et al., "Relations Between Liposomes and Biomembranes", Annals New York Acad. Sci., 1978, 308, 85-99.

Other Reference Publication (106):
Gabizon et al., "Liposome formulations with prolonged circulation time in blood and enhanced uptake by tumors", Proc. Natl. Acad. Sci. USA, 1988, 85, 6949-6953.

Other Reference Publication (107):
Garelli et al., "Incorporation of new amphiphilic perfluoroalkylated bipyridine platinum and palladium complexes into liposomes: stability and structure-incorporation relationships", Biochim. et Biophys. Acta, 1992, 1127, 41-48.

Other Reference Publication (112):
May et al., "Cationic Liposomes Enable Bovine Herpesvirus Type 2 DNA to Infect Cells", Acta virol., 1991, 35, 107.

Other Reference Publication (114):
Sato et al., "Recent Aspects in the Use of Liposomes in Biotechnology and Medicine", Prog. Lipid Res., 1992, 31(4), 345-372.

Other Reference Publication (117):
Trubetskoy et al. "Cationic liposomes enhance targeted delivery and expression of exogenous DNA mediated by N-terminal modified poly(L-lysine) -antibody conjugate in mouse lung endothelial cells", Biochim. et Biophys. Acta, 1992, 1131, 311-313.

Other Reference Publication (120):
Woodle et al., "Versatility in lipid compositions showing prolonged circulation with sterically stabilized liposomes", Biochim. et Biophys. Acta, 1992, 1105, 193-200.

Other Reference Publication (121):
Zhou et al., "Targeted delivery of DNA by liposomes and polymers", J. Control. Release, 1992, 19, 269-274.

Other Reference Publication (127):
Santaella et al., "Extended In Vivo Blood Circulation Time of Fluorinated Liposomes", FEBS 13463, 1993, 336(3), 481-484.

Other Reference Publication (136):
Frezard et al., "Permeability and stability in buffer and in human serum of fluorinated phospholipid-based liposomes", Biochim. et Biophys. Acta, 1994, 1192, pp. 61-70.

Other Reference Publication (141):
Yeung et al., "Preparation of Microencapsulated Liposomes", J. Microencapsulation, 1988, 5(4), 331-337.

Other Reference Publication (151):
Unger et al., "Liposomal MR Contrast Agents", J. Liposome Research, 1994, 4(2), 811-834.

Other Reference Publication (170):
Frezard, F., et al., "Fluorinated phosphatidylcholine-based liposomes: H.sup.+ /Na.sup.+ permeability, active doxorubicin encapsulation and stability in human serum," Biochimica et Biophysica Acta 1194, XP-000990899, 1994, 61-68.

Other Reference Publication (173):
Riess, J.G., "Introducing a new element-fluorine-into the liposomal membrane," J. Liposome Research, XP 000525914, 1995, 5(3), 413-430.

Other Reference Publication (174):
Santaella, C., et al., "Extended in vivo blood circulation time of fluorinated liposomes," XP-000990861, FEBS 13463, XP-000990861, 1993, 336(3), 481-484.

Other Reference Publication (175):
Trevino, L., et al., "Incorporation of a perfluoroalkylalkane (R.sub.F R.sub.H) into the phospholipid bilayer of DMPC liposomes results in greater encapsulation stability," J. Liposome Research, XP 000457303, 1994, 4(2), 1017-1028.

WEST

End of Result Set

Generate Collection Print

L5: Entry 1 of 1 File: USPT Sep 7, 1982

DOCUMENT-IDENTIFIER: US 4348384 A
TITLE: Pharmaceutical composition for oral administration containing coagulation factor VIII or IX

Detailed Description Text (6):
In the same manner as described in Example 1, yolk lecithin (2 g) containing 10% of phosphatidic acid is dissolved in ethanol (40 ml) and the solution is concentrated under reduced pressure in a one-liter flask to deposit the lecithin as a thin layer on the inner wall of the flask. After drying under reduced pressure, a phosphate buffer solution (pH 7.0, 50 ml) containing coagulation factor VIII (3,000 units) and aprotinin (150 thousand units) is added thereto, and the flask is lightly shaken to obtain a suspension of liposomes. The suspension of liposomes is entered into a centrifugal tube and cooled to 10.degree. C. and then centrifuged at 27,000 G for 20 minutes, by which creamy liposomes are obtained at the upper part. The transparent aqueous layer is again treated with lecithin and the mixture is treated in the flask in the same manner as above. The procedure is repeated three times. The creamy liposomes obtained in the above three times procedures are combined and suspended in physiological saline (50 ml) and thereto is added an appropriate amount of distilled water and the liposomes are uniformly dispersed therein. The mixture is rapidly frozen by cooling at -40.degree. C. to -60.degree. C. and lyophilized under reduced pressure with sublimating water. (During the lyophilization, sugars may be added to the liposome particles as a stabilizer)

Detailed Description Text (22):
In the same manner as described in Example 5, yolk lecithin (1 g) containing 10% of phosphatidic acid or calcium phosphatidate is dissolved in ethanol (20 ml), and the solution is concentrated under reduced pressure in a one-liter flask to deposit the lecithin as a thin layer on the inner wall of the flask. After drying under reduced pressure, a phosphate buffer solution (pH 7.0) containing calcium ion and coagulation factor IX (400 units) and aprotinin (50 thousand units), and the flask is lightly shaken to obtain a suspension of liposomes. The suspension of liposomes is entered into a centrifugal tube and cooled to 10.degree. C. and then centrifuged at 27,000 G for 20 minutes, by which creamy liposomes are obtained at the upper part. The aqueous layer is again treated with lecithin and the mixture is treated in the flask in the same manner as above. The procedure is repeated three times. The creamy liposomes obtained in the above three times procedures are combined and suspended in physiological saline (30 ml) and thereto is further added an appropriate amount of distilled water, and the liposomes are uniformly dispersed therein. The mixture is rapidly frozen by cooling at -40.degree. to -60.degree. C. and lyophilized under reduced pressure with sublimating water. (During the lyophilization, stabilizers such as sugars may be added to the liposome particles)

WEST Search History

DATE: Monday, July 21, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L5	$sublim$ same liposome$ same sugar$	1	L5
L4	L3 and sugars	132	L4
L3	$sublim$ and liposome$	243	L3
L2	l1 and $sublima$	0	L2
L1	trehalose adj5 liposome$	34	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 30 of 34 returned.

☐ 1. Document ID: US 6497898 B1

L1: Entry 1 of 34 File: USPT Dec 24, 2002

US-PAT-NO: 6497898
DOCUMENT-IDENTIFIER: US 6497898 B1

TITLE: Surfactant, and an emulsion-type cosmetic composition and a lipsome containing said surfactant

DATE-ISSUED: December 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ikemoto; Takeshi	Kanagawa			JP
Minamino; Hiromi	Kanagawa			JP
Sumida; Yasushi	Kanagawa			JP
Inoue; Yoh-ichi	Kanagawa			JP

US-CL-CURRENT: 424/450; 424/400, 424/401

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6455088 B1

L1: Entry 2 of 34 File: USPT Sep 24, 2002

US-PAT-NO: 6455088
DOCUMENT-IDENTIFIER: US 6455088 B1

TITLE: Peptide/lipid complex formation by co-lyophilization

DATE-ISSUED: September 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dasseux; Jean-Louis	Brighton	MI	48116	

US-CL-CURRENT: 426/450; 514/12, 514/13, 514/2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6451338 B1

L1: Entry 3 of 34 File: USPT Sep 17, 2002

US-PAT-NO: 6451338
DOCUMENT-IDENTIFIER: US 6451338 B1

TITLE: Liposomes containing particulate materials

DATE-ISSUED: September 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gregoriadis; Gregory	Northwood			GB
Antimisiaris; Sophia George	Patras			GB
Gursel; Ishan	Ankara			GB

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 264/4.6, 424/204.1, 424/234.1, 424/240.1, 424/246.1, 424/258.1, 424/265.1, 424/269.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

---

☐ 4. Document ID: US 6348214 B1

L1: Entry 4 of 34 File: USPT Feb 19, 2002

US-PAT-NO: 6348214
DOCUMENT-IDENTIFIER: US 6348214 B1

TITLE: Materials and methods for making improved liposome compositions

DATE-ISSUED: February 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Onyuksel; Hayat	Western Springs	IL		
Rubinstein; Israel	Highland Park	IL		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 264/4.6, 514/2, 514/21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 5. Document ID: US 6322809 B1

L1: Entry 5 of 34 File: USPT Nov 27, 2001

US-PAT-NO: 6322809
DOCUMENT-IDENTIFIER: US 6322809 B1

TITLE: Liposomes containing particulate materials

DATE-ISSUED: November 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gregoriadis; Gregory	Northwood			GB
Antimisiaris; Sophia George	FR-Patra			GR
Gursel; Ihsan	Ankara			TR

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 264/4.6, 424/234.1, 424/240.1, 424/246.1, 424/258.1, 424/93.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 6. Document ID: US 6319517 B1

L1: Entry 6 of 34 File: USPT Nov 20, 2001

US-PAT-NO: 6319517
DOCUMENT-IDENTIFIER: US 6319517 B1

TITLE: Pharmaceutical preparation comprising lyophilized liposomes encapsulating an active principle which is highly insoluble in water, and the process for preparing the said preparation

DATE-ISSUED: November 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cavallo; Giovanni	Ostia			IT
Marchitto; Leonardo	Cupra Marittima			IT

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 424/1.21, 424/417, 424/9.321, 424/9.51, 514/2, 514/21, 514/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 7. Document ID: US 6287590 B1

L1: Entry 7 of 34 File: USPT Sep 11, 2001

US-PAT-NO: 6287590
DOCUMENT-IDENTIFIER: US 6287590 B1
**** See image for Certificate of Correction ****

TITLE: Peptide/lipid complex formation by co-lyophilization

DATE-ISSUED: September 11, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dasseux; Jean-Louis	Mannheim			DE

US-CL-CURRENT: 424/450; 514/12, 514/13, 514/2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 8. Document ID: US 6221575 B1

L1: Entry 8 of 34 File: USPT Apr 24, 2001

US-PAT-NO: 6221575
DOCUMENT-IDENTIFIER: US 6221575 B1

TITLE: Methods for producing dried storage-stable platelets and compositions obtained thereby

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roser; Bruce J.	Cambridge			GB
Menys; Valentine	Cherry Hinton			GB
Grandage; Lynda	Haslingfield			GB
Phipps; Diana	Nassington			NL

US-CL-CURRENT: 435/2; 424/532, 435/374, 436/18, 536/123.13

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 9. Document ID: US 6197333 B1

L1: Entry 9 of 34 File: USPT Mar 6, 2001

US-PAT-NO: 6197333
DOCUMENT-IDENTIFIER: US 6197333 B1

TITLE: Materials and methods for making improved liposome compositions

DATE-ISSUED: March 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Onyuksel; Hayat	Western Springs	IL		
Rubinstein; Israel	Highland Park	IL		

US-CL-CURRENT: 424/450; 424/401

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 10. Document ID: US 6165778 A

L1: Entry 10 of 34 File: USPT Dec 26, 2000

US-PAT-NO: 6165778
DOCUMENT-IDENTIFIER: US 6165778 A

TITLE: Reaction vessel agitation apparatus

DATE-ISSUED: December 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kedar; Haim	Palo Alto	CA		

US-CL-CURRENT: 435/289.1; 366/110, 366/111, 366/211, 422/104, 435/287.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 11. Document ID: US 5922350 A

L1: Entry 11 of 34 File: USPT Jul 13, 1999

US-PAT-NO: 5922350
DOCUMENT-IDENTIFIER: US 5922350 A

TITLE: Methods of dehydrating, storing and rehydrating liposomes

DATE-ISSUED: July 13, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Cullis; Pieter R.	Vancouver			CA
Bally; Marcel B.	Vancouver			CA
Fountain; Michael W.	Griggstown	NJ		
Ginsberg; Richard S.	Monroe	NJ		
Hope; Michael J.	Vancouver			CA
Madden; Thomas D.	Vancouver			CA
Schieren; Hugh P.	Yardley	PA		
Jablonski; Regina L.	Trenton	NJ		

US-CL-CURRENT: 424/450; 264/4.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 12. Document ID: US 5837279 A

L1: Entry 12 of 34 File: USPT Nov 17, 1998

US-PAT-NO: 5837279
DOCUMENT-IDENTIFIER: US 5837279 A

TITLE: Encapsulation of ionizable agents in liposomes

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Cullis; Pieter R.	Vancouver			CA
Bally; Marcel B.	Vancouver			CA
Fountain; Michael W.	Griggstown	NJ		
Ginsberg; Richard S.	Monroe	NJ		
Hope; Michael J.	Vancouver			CA
Madden; Thomas D.	Vancouver			CA
Schieren; Hugh P.	Yardley	PA		
Jablonski; Regina L.	Trenton	NJ		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 264/4.6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 13. Document ID: US 5773006 A

L1: Entry 13 of 34 File: USPT Jun 30, 1998

US-PAT-NO: 5773006
DOCUMENT-IDENTIFIER: US 5773006 A

TITLE: Lipsome containing IL-2

DATE-ISSUED: June 30, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anderson; Peter M.	St. Louis Park	MN		
Leonard; Arnold S.	Minneapolis	MN		
Ochoa; Augusto C.	Minneapolis	MN		
Loeffler; Cynthia	Woodbury	MN		

US-CL-CURRENT: 424/195.11; 424/155.1, 424/184.1, 424/200.1, 424/208.1, 424/234.1, 424/417, 424/423, 424/450, 424/812, 424/85.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 14. Document ID: US 5753262 A

L1: Entry 14 of 34 File: USPT May 19, 1998

US-PAT-NO: 5753262
DOCUMENT-IDENTIFIER: US 5753262 A
**** See image for Certificate of Correction ****

TITLE: Cationic lipid acid salt of 3beta[N- (N', N'-dimethylaminoethane) - carbamoyl]cholestrol and halogenated solvent-free preliposomal lyophilate thereof

DATE-ISSUED: May 19, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wyse; Joseph W.	The Woodlands	TX		
Warner; Charles D.	The Woodlands	TX		

US-CL-CURRENT: 424/450; 435/458, 436/71, 552/545

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 15. Document ID: US 5650152 A

L1: Entry 15 of 34 File: USPT Jul 22, 1997

US-PAT-NO: 5650152
DOCUMENT-IDENTIFIER: US 5650152 A

TITLE: Liposome immunoadjuvants containing IL-2

DATE-ISSUED: July 22, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anderson; Peter M.	St. Louis Park	MN		
Leonard; Arnold S.	Minneapolis	MN		
Ochoa; Augusto C.	Minneapolis	MN		
Loeffler; Cynthia	Woodbury	MN		

US-CL-CURRENT: 424/195.11; 424/155.1, 424/184.1, 424/200.1, 424/201.1, 424/204.1, 424/208.1, 424/234.1, 424/275.1, 424/283.1, 424/423, 424/450, 424/812, 424/85.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 16. Document ID: US 5648090 A

L1: Entry 16 of 34 File: USPT Jul 15, 1997

US-PAT-NO: 5648090
DOCUMENT-IDENTIFIER: US 5648090 A
**** See image for Certificate of Correction ****

TITLE: Liposome encapsulated toxol and a method of using the same

DATE-ISSUED: July 15, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rahman; Aquilur	Gaithersburg	MD		
Rafaeloff; Rafael	Tel-Aviv			IL
Husain; Syed Rafat	Gaithersburg	MD		

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 17. Document ID: US 5639603 A

L1: Entry 17 of 34 File: USPT Jun 17, 1997

US-PAT-NO: 5639603
DOCUMENT-IDENTIFIER: US 5639603 A

TITLE: Synthesizing and screening molecular diversity

DATE-ISSUED: June 17, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dower; William J.	Menlo Park	CA		
Barrett; Ronald W.	Sunnyvale	CA		
Gallop; Mark A.	Palo Alto	CA		
Needels; Michael C.	Oakland	CA		

US-CL-CURRENT: 435/6; 530/334, 530/335, 536/25.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 18. Document ID: US 5578320 A

L1: Entry 18 of 34 File: USPT Nov 26, 1996

US-PAT-NO: 5578320
DOCUMENT-IDENTIFIER: US 5578320 A

TITLE: Method of dehydrating liposomes using protective sugars

DATE-ISSUED: November 26, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Cullis; Pieter R.	Vancouver			CA
Bally; Marcel B.	Vancouver			CA
Fountain; Michael W.	Griggstown	NJ		
Ginsberg; Richard S.	Monroe	NJ		
Hope; Michael J.	Vancouver			CA
Madden; Thomas D.	Vancouver			CA
Schieren; Hugh P.	Yardley	PA		
Jablonski; Regina L.	Trenton	NJ		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 264/4.6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 19. Document ID: US 5424073 A

L1: Entry 19 of 34 File: USPT Jun 13, 1995

US-PAT-NO: 5424073
DOCUMENT-IDENTIFIER: US 5424073 A

TITLE: Liposome encapsulated taxol and a method of using the same

DATE-ISSUED: June 13, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rahman; Aquilur	Gaithersburg	MD		
Rafaeloff; Rafael	Tel-Aviv			IL
Husain; Syed R.	Gaithersburg	MD		

US-CL-CURRENT: 424/450; 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 20. Document ID: US 5409698 A

L1: Entry 20 of 34 File: USPT Apr 25, 1995

US-PAT-NO: 5409698
DOCUMENT-IDENTIFIER: US 5409698 A
**** See image for Certificate of Correction ****

TITLE: Liposome immunoadjuvants containing IL-2

DATE-ISSUED: April 25, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anderson; Peter M.	St. Louis Park	MN		
Leonard; Arnold S.	Minneapolis	MN		
Ochoa; Augusto C.	Minneapolis	MN		
Loeffler; Cynthia	Woodbury	MN		

US-CL-CURRENT: 424/85.2; 424/283.1, 424/423, 424/450, 424/812

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 21. Document ID: US 5180713 A

L1: Entry 21 of 34 File: USPT Jan 19, 1993

US-PAT-NO: 5180713
DOCUMENT-IDENTIFIER: US 5180713 A

TITLE: Stabilized liposome/amphotercin B composition and method

DATE-ISSUED: January 19, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Abra; Robert	San Francisco	CA		
Szoka; Francis C.	San Francisco	CA		

US-CL-CURRENT: 514/31; 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 22. Document ID: US 5059518 A

L1: Entry 22 of 34 File: USPT Oct 22, 1991

US-PAT-NO: 5059518
DOCUMENT-IDENTIFIER: US 5059518 A

TITLE: Stabilized lyophilized mammalian cells and method of making same

DATE-ISSUED: October 22, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kortright; Kenneth H.	Davie	FL		
Raynor; Robert H.	Miramar	FL		
Healy, Jr.; Stephen F.	Miami	FL		

US-CL-CURRENT: 435/6; 435/2, 435/243, 435/260, 435/29, 435/34, 435/372.2, 435/372.3, 435/7.21, 435/7.23, 435/7.24, 436/10, 436/63, 436/64, 436/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 23. Document ID: US 4927571 A

L1: Entry 23 of 34 File: USPT May 22, 1990

US-PAT-NO: 4927571
DOCUMENT-IDENTIFIER: US 4927571 A
**** See image for Certificate of Correction ****

TITLE: Preparation of injectable doxorubicin/liposome suspension

DATE-ISSUED: May 22, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huang; Anthony H.	Sunnyvale	CA		
Krishnan; Satya	Mountain View	CA		

US-CL-CURRENT: 264/4.3; 424/450, 428/402.2, 436/829, 514/893, 514/894, 514/908

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 24. Document ID: US 4897353 A

L1: Entry 24 of 34 File: USPT Jan 30, 1990

US-PAT-NO: 4897353
DOCUMENT-IDENTIFIER: US 4897353 A

TITLE: Cryogenic protection of phosphofructokinase using amino acids and zinc ions

DATE-ISSUED: January 30, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Carpenter; John F.	David	CA		
Hand; Steven C.	Louisville	CO		
Crowe; Lois M.	Davis	CA		
Crowe; John H.	Davis	CA		

US-CL-CURRENT: 435/188; 435/194, 435/814

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 25. Document ID: US 4880635 A

L1: Entry 25 of 34 File: USPT Nov 14, 1989

US-PAT-NO: 4880635
DOCUMENT-IDENTIFIER: US 4880635 A
**** See image for Certificate of Correction ****
**** See image for Reexamination Certificate ****

TITLE: Dehydrated liposomes

DATE-ISSUED: November 14, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Janoff; Andrew S.	Yardley	PA		
Cullis; Pieter R.	Vancouver			CA
Bally; Marcel B.	Vancouver			CA
Fountain; Michael W.	Griggstown	NJ		
Ginsberg; Richard S.	Monroe	NJ		
Hope; Michael J.	Vancouver			CA
Madden; Thomas D.	Vancouver			CA
Schieren; Hugh P.	Yardley	PA		
Jablonski; Regina L.	Trenton	NJ		

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 26. Document ID: US 4857319 A

L1: Entry 26 of 34 File: USPT Aug 15, 1989

US-PAT-NO: 4857319
DOCUMENT-IDENTIFIER: US 4857319 A

TITLE: Method for preserving liposomes

DATE-ISSUED: August 15, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Crowe; John H.	Davis	CA		
Crowe; Lois M.	Davis	CA		

US-CL-CURRENT: 424/94.1; 424/94.4, 435/26, 435/4, 436/829, 514/2, 514/3, 514/44, 514/579, 514/646, 514/76, 514/77, 514/78

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 27. Document ID: US 4806343 A

L1: Entry 27 of 34 File: USPT Feb 21, 1989

US-PAT-NO: 4806343
DOCUMENT-IDENTIFIER: US 4806343 A

TITLE: Cryogenic protectant for proteins

DATE-ISSUED: February 21, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Carpenter; John F.	Davis	CA		
Hand; Steven C.	Lafayette	LA		
Crowe; John H.	Davis	CA		
Crowe; Lois M.	Davis	CA		

US-CL-CURRENT: 424/450; 264/4.3, 34/287, 424/94.3, 428/402.2, 435/188, 436/829, 514/1, 514/3, 514/6, 514/777, 514/971

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 28. Document ID: US 4766046 A

L1: Entry 28 of 34 File: USPT Aug 23, 1988

US-PAT-NO: 4766046
DOCUMENT-IDENTIFIER: US 4766046 A

TITLE: Stabilized liposome/amphotericin composition and method

DATE-ISSUED: August 23, 1988

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Abra; Robert	San Francisco	CA		
Szoka; Francis C.	San Francisco	CA		

US-CL-CURRENT: 424/450; 264/4.3, 264/4.6, 436/829, 514/31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

☐ 29. Document ID: JP 01075421 A

L1: Entry 29 of 34 File: JPAB Mar 22, 1989

PUB-NO: JP401075421A
DOCUMENT-IDENTIFIER: JP 01075421 A
TITLE: FREEZE-DRIED PREPARATION OF LIPOSOME CONTAINING ALPHA,ALPHA-TREHALOSE TRIMYCOLIC ACID ESTER

PUBN-DATE: March 22, 1989

INVENTOR-INFORMATION:

NAME	COUNTRY
KATO, TAKAYOSHI	
YOKOI, FUSA	

INT-CL (IPC): A61K 31/72; A61K 9/10; A61K 31/72; C07H 13/06

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Clip Img | Image

☐ 30. Document ID: WO 9836736 A1

L1: Entry 30 of 34 File: EPAB Aug 27, 1998

PUB-NO: WO009836736A1
DOCUMENT-IDENTIFIER: WO 9836736 A1
TITLE: PHARMACEUTICAL PREPARATION COMPRISING LYOPHILIZED LIPOSOMES ENCAPSULATING AN ACTIVE PRINCIPLE WHICH IS HIGHLY INSOLUBLE IN WATER, AND THE PROCESS FOR PREPARING THE SAID PREPARATION

PUBN-DATE: August 27, 1998

INVENTOR-INFORMATION:

NAME	COUNTRY
CAVALLO, GIOVANNI	IT
MARCHITTO, LEONARDO	IT

INT-CL (IPC): A61 K 9/127; A61 K 38/13; A61 K 31/41
EUR-CL (EPC): A61K009/127

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

Generate Collection | Print

Terms	Documents
trehalose adj5 liposome$	34

Display Format: - Change Format

Previous Page Next Page